Method for Angiographically Guided Fine-Needle Diathermy in the Treatment of Corneal Neovascularization

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Purpose: To describe a method to assess corneal neovascular (CoNV) complexes and identify feeder vessels for selective arterial fine-needle diathermy (FND).

Methods: In patients with CoNV, color photography and corneal indocyanine green angiography (ICGA) and fluorescein angiography are performed. After injection of indocyanine green and sodium fluorescein dye, videography and single-frame images of the region of interest are recorded. Videography is used to measure the time to leakage to assess vessel maturity to guide medical treatment and to discern afferent from efferent vessels. Single-frame images are then selected to locate the number of afferent vessels for surgery, which are selectively cut with a 25-gauge marked needle for the application of FND.

Results: Angiography using fluorescein and indocyanine green allows the characterization of CoNV based on assessment of both morphologic (ICGA) and functional (fluorescein angiography) parameters. The time to leakage of fluorescein dye provides important functional information on vessel maturity and helps discern whether medical treatment should be followed before surgical. ICGA allows the identification and delineation of afferent feeder vessels even in the presence of corneal opacities affecting biomicroscopic visibility. Colocalizing the afferent vessel to a visible venous landmark or branch is helpful for placement of the incision and application of FND. Using the described approach, angiographically identified feeder vessels can be selectively treated by FND with minimal thermal energy applied to the corneoscleral limbus.

Conclusions: The described method for angiographically guided assessment of CoNV is a useful approach for guiding the medical and surgical treatment of CoNV.

Key Words: corneal neovascularization, fine-needle diathermy, angiography, anterior segment examination

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Corneal neovascularization (CoNV) is a global health problem. It is estimated that 1.4 million people per year develop CoNV, 12% of whom suffer subsequent loss of vision.[1] Additionally, vascularization of the recipient cornea before transplantation is a leading cause for earlier and more marked graft rejection.[2]

Several medical and surgical treatment approaches for the management of CoNV have been investigated with varying degrees of clinical success. VEGF plays a prominent role in corneal angiogenesis, and selective inhibitors of VEGF have been applied successfully in treating active CoNV, targeting predominantly immature vessels.[3] Although surgical treatment such as fine-needle diathermy (FND) has become popular for the treatment of more established vessels in CoNV,[4] potential adverse effects need to be considered. These include potential damage to the corneal endothelium and the limbal epithelial stem cell niche and, particularly when not applied selectively, may lead to inflammation, scarring, and varying degrees of irregular corneal astigmatism. Until recently, the most widely used method was described by Faraj et al,[5] using unipolar diathermy applied to all areas of visible blood vessels through a 3/8 circle-side–cutting, single-armed needle attached to a 10-0 monofilament nylon suture. This technique, however, is associated with extensive application of thermal energy to all corneal structures including the deep peripheral corneal stroma, potentially damaging the corneal endothelium beneath and surrounding the coagulation site similar to that observed after radial thermokeratoplasty. Additional adverse effects include the modification of the corneal curvature and collagen shrinkage with potential damage to adjacent corneal stroma.[6–9] Long-term effects of diathermy to the cornea and the corneoscleral limbal stem cell niche remain to be clarified. The process of corneal diathermy itself may be a stimulus for further CoNV by secondary release of proangiogenic factors.[10] It would, therefore, seem reasonable to try and minimize the application of FND to the cornea. We recently reported the results of selective FND to the afferent vessel(s)[11,12] and describe below the protocol for this angiography-guided treatment approach.

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PROTOCOL

Imaging Section (Color Photography, Fluorescein Angiography, and Indocyanine Green Angiography)

Color images are captured using a slit-lamp–mounted digital system (SL-D Digital Slit Lamp; Topcon, Tokyo, Japan) at 10 to 25-power magnification. An HRA2 Scanning Laser Ophthalmoscope (Heidelberg Engineering, Heidelberg, Germany) with a 20° imaging lens set at 34 diopters is used for indocyanine green angiography (ICGA) and fluorescein angiography as previously described.[13,14] It is important to note that in the healthy state, the vasculature surrounding the peripheral cornea and limbus fills in a distinctive pattern with the inferior (I) quadrant filling first, followed by the superior (S), nasal (N), and finally temporal (T) quadrants (the ISNT rule).[13] In addition, the age and cardiovascular status are important considerations in determining the time elapsed before commencement of the video recording for the appearance of dye in the afferent vessels. In a young person, dye would be expected to be seen approximately 10 seconds after injection, whereas in an elderly person the dye may not appear until after 25 seconds. After injection of 5 mL of ICG dye (5 mg/mL; Pulsion Medical Systems, Feldkirchen, Germany), videography is performed for 25 seconds (see Video, Supplemental Digital Content 1, http://links.lww.com/ICO/A409). ICGA provides excellent vessel resolution particularly in areas of corneal scarring, infiltrate, or edema (Figs. 1C, F). Single-frame ICGA images of the region of interest of the cornea and limbus capturing corneal blood vessel fluorescence are taken every 3 to 5 seconds for 3 minutes, followed by late images at 5 and 10 minutes. An intravenous injection of 3 mL of 20% sodium fluorescein (Martindale Pharmaceuticals, Essex, United Kingdom) is then given and the videography repeated. Fluorescein angiography provides important information on time to leakage, which is important to assess vessel maturing and late reuptake by lymphatics (Figs. 1B, E). During the acquisition of single-frame ICGA and Fluorescein angiography images, high-resolution mode with eye tracking, automatic, real-time software is used. Single-frame stereoscopic images can provide useful information regarding the location and depth of the vessel(s).

Image Analysis

Video analysis allows the identification of the location and number of afferent vessels crossing the peripheral cornea and limbus and measurement of the time to leakage of fluorescein. The extent of leakage aids in the clinical decision between medical and surgical treatment, time and extent of leakage being an indirect indicator of vessels maturity. Vessels with early and intense leakage may still be responsive to topical steroid treatment or subconjunctival injection of VEGF inhibitors, potentially without the need for FND.[15] The identified afferent vessels are colocalized on color photographs using visible landmarks such as a vessel branch to guide selective arteriolar FND.[9,16,17] Semiautomated programs using Matlab R14 (The MathWorks Inc, Natick, MA) are helpful in analyzing vessel parameters such as area of CoNV and vessel length, diameter, branch points, and tortuosity, which are useful information for monitoring outcome.[13,14] It is important to note that the afferent (arterial) vessels usually lie below and deeper in the corneal stroma to the associated venules, are often not visible on color images, and may not be easily discernible on slit-lamp biomicroscopy. On colocalizing the afferent vessel to a visible larger venule, for example, the distance from the venous landmark or branch allows the surgeon to place a mark as described below.

Fine-Needle Diathermy

Afferent and efferent vessels are identified on videography. The former are labeled on a representative angiographic image and a corresponding color photograph (Fig. 1). The annotated images are used as a reference to mark the afferent vessel(s) with an inked needle. Using slit-lamp biomicroscopy, a partial-thickness incision is made under topical anesthesia, using a 25-gauge needle on a 1-mL syringe into the posterior stroma over the identified afferent vessel(s) either at the limbus or at the level of marginal corneal arcades. A 25-gauge needle is preferred to a blade as it causes less obscuration of structures and can be more easily advanced at the slip lamp under direct vision to the deep stromal feeder vessels without necessarily causing bleeding from superficial venous vessels. Afferent vessels may be hard to distinguish despite their known location, because they are of thinner caliber and the fast intravascular flow may not allow the distinction of cell traffic direction. Therefore, indirect illumination is used to obtain optimal conditions for the identification of these vessel characteristics. If the afferent vessel is transected, an interruption of red blood cell traffic becomes evident in all the visible vessels, which are mainly the efferent vessels (veins). Under the operating microscope, an Ellman MH-EL-A2D fine-wire electrolysis needle is then applied into the incision. Energy is delivered using a unipolar approach by a Surgitron Dual RF machine (Ellman International Inc, Oceanside, NY) at the lowest setting (1 joule/s) until a visible blanching of the cornea around the afferent vessel is seen and segmentation of the blood flow is noticed in the larger efferent vessels if not already present. Patients receive prednisolone 1% eye drops 4 times a day for 4 weeks and an antimicrobial 4 times a day for 1 week.

DISCUSSION

Slit-lamp assessment of CoNV, although essential, needs to be complemented by angiography, as only the latter is able to reproducibly provide information to assess the extent and activity to ultimately guide the treatment.[14] Tissue cauterization such as FND is not without risk and should be kept to a minimum. In addition, the long-term consequences of FND on limbal epithelial stem cell function and local endothelial cell survival are not yet fully understood. Corneal diathermy itself may be a stimulus for further CoNV by secondary release of proangiogenic factors.[10] Feldman et al[6] showed that radial thermokeratoplasty caused damage to the corneal endothelium beneath and surrounding the coagulation

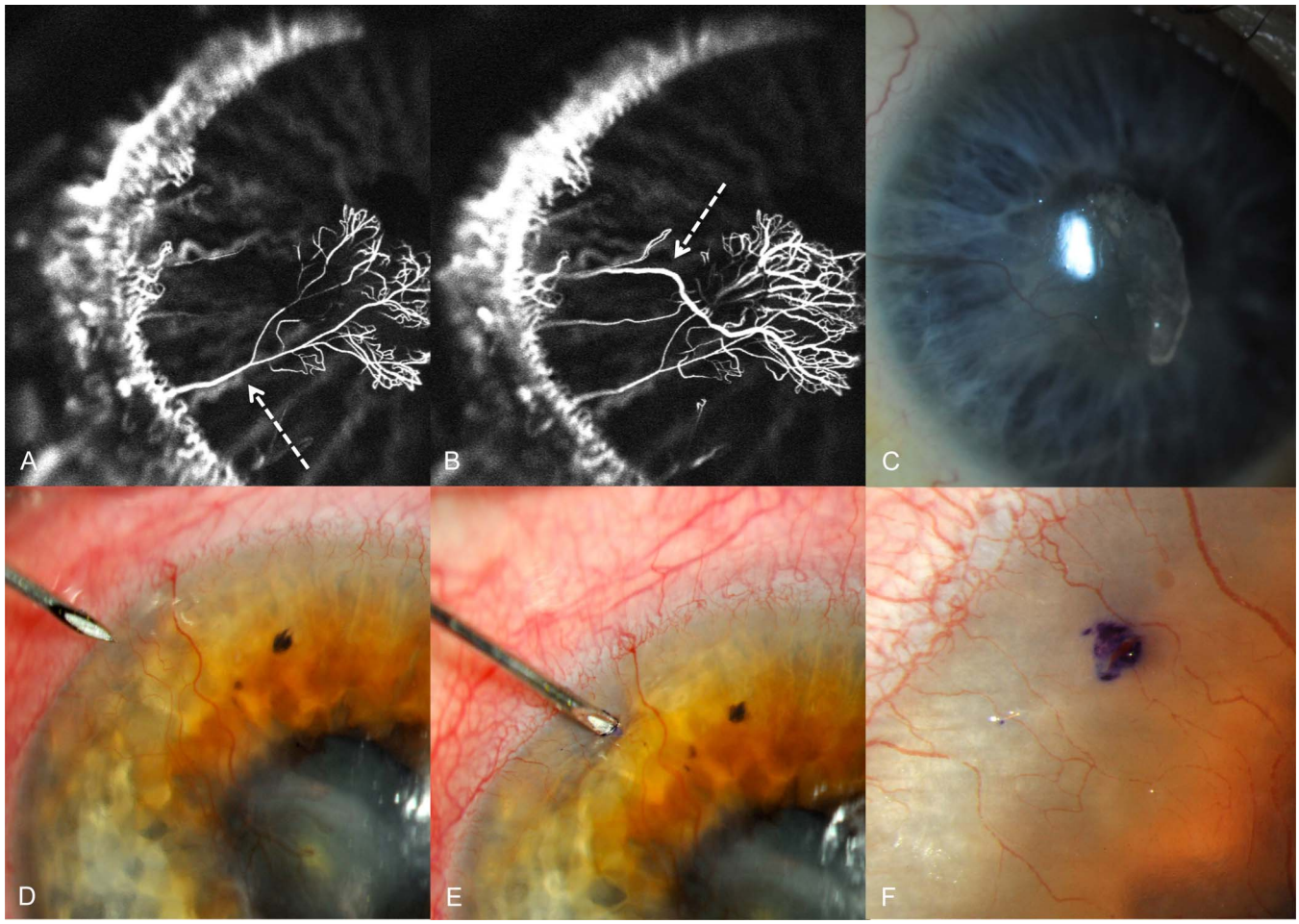

FIGURE 1. Graphic illustration of the preparation for angiography-guided selective arteriolar FND of CoNV. A, Arterial phase (24 seconds) of ICGA showing the afferent feeder vessel of CoNV (arrow). B, Venous phase (21 seconds) of ICGA showing the efferent vessels of CoNV (arrow). C, Color photograph of CoNV to identify afferent vessels from comparative analysis with angiographic studies. D–F, In a different patient, the afferent vessel is cut with an ink-marked 25-gauge needle for subsequent selective arteriolar FND.

site. The corneal heating also modifies corneal curvature and may lead to irregular astigmatism.[8] In particular, collagen shrinkage with potential damage to adjacent corneal stroma has been reported.[8] Nonselective application will increase inflammation, which may itself prejudice subsequent corneal transplant survival. Therefore, the amount of tissue cauterization should be minimized. This is of particular importance if FND is performed for preconditioning a recipient bed for a future corneal graft.

The described cut-down technique is preferred over the use of a 10-0 needle because the created cut allows verification of blood flow interruption before actual diathermy. Additionally, the use of a syringe at the slit lamp allows better depth perception, flow observation, and cut orientation compared with a surgical microscope.

Cursiefen et al reported that arterioles tend to comprise less than 1% of the vessel area in CoNV, making them a feasible target in the surgical treatment of CoNV.[18] Biomicroscopic distinction of afferent and efferent vessels can be very challenging even when aided by the patient's pulse, and the visible area of pathologic vessels on slit-lamp examination does not reflect the true extent of CoNV.[16] Corneal angiography enables quantification of CoNV, vessel leakage, and identification of afferent or feeder vessels for selective treatment, thereby lessening the risks associated with this type of treatment.[12,13] Although the efficacy of FND in the treatment of corneal hematic vessels is evident, its effect on corneal lymphatic or plasma vessels in CoNV as recently shown by our group remains to be investigated.[12,16,17] Optical coherence tomography (OCT) angiography may offer an additional complimentary approach, but at present, it is not able to distinguish between afferent and efferent vessels.[19–21] Although OCT angiography is likely to be a very useful adjunct, the current methods are limited in resolution to an axial and lateral resolution of approximately 5 to 8 μm and 20 to 20 μm[22] so that components of small vessels such as capillary loops may not be discernible. In addition, OCT relies on red blood cell movement[23–25] and is therefore dependent and influenced by cell number and velocity and[22] is therefore not sensitive to acellular flow, in particular leakage. The latter is of particular importance as limiting initial

treatment to the application of antiangiogenic factors such as VEGF inhibitors may be the better choice if less mature or immature vessels predominate.[3]

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